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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,134	10/20/2002	Chandrasekhar Satishchandran	NUCL-001/01US 306512-2006	5538

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,134	SATISHCHANDRAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-174* is/are pending in the application.

4a) Of the above claim(s) *68-106,169 and 170* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107-168 and 171-174* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/06/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 02/06/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 09/07/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 68-174 are pending. Claims 107-168 and 171-174 are currently under examination. Claims 68-106 and 169-170 are withdrawn as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement filed 02/06/2008 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the foreign patent documents indicated as document Nos. 85 and 113 have not been translated. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Further, several of the foreign patent documents were not translated but the English translation of the abstract was included and therefore those abstracts have been considered as indicated on the PTO 1449.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing

element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Response to Declaration

The declaration filed on 02/06/2008 under 37 CFR 1.132 is considered but is insufficient overcome the rejections of record for the reasons stated below.

Response to Arguments

Re: Claim Rejections - 35 USC § 103

The rejection of claims 107-168 and 171-174 under 35 U.S.C. 103(a) as being unpatentable over Werther et al. (cited on PTO Form 892 filed 08/07/2006), Fire et al. (cited on PTO Form 892 filed 08/07/2006), Heifetz et al (cited on PTO Form 892 filed 08/07/2006), Calabretta et al. (US Patent No. 5,734,039) and Thompson et al. (cited on PTO Form 892 filed 08/07/2006) is maintained for the reasons of record in the Office action mailed 03/08/2007 and 09/07/2007 (with respect to claim 174).

Applicant's arguments filed 02/06/2008 have been fully considered but they are not persuasive. Applicants argue the skilled artisan would not have been motivated to substitute the double stranded RNA molecules disclosed in Fire et al. and Heifetz et al. for the antisense sequences in the constructs disclosed by Werther et al. and Calabretta et al. Applicants argue that although Fire et al. "suggests that double stranded RNA might be useful for inhibition of gene expression in mammals, it does not exemplify or enable such a use." Applicants argues the skilled artisan, at the time the invention was

made, would not use long double stranded RNA molecules because they elicit a PKR response that results in nonspecific inhibition of gene expression and submits a declaration by Dr. McCallus which supports these views. Thus, Applicant argues, the art effectively taught away from using double stranded RNA molecules as claimed in the present invention for sequence specific gene silencing in mammalian cells.

In response to Applicants assertion that Fire et al. does not exemplify or enable use of dsRNA in mammalian cells, it is not disputed that Fire et al. did not exemplify his invention in human cells. However, just because Fire et al. did not reduce to practice his invention does not mean the invention was not enabled. Since the issuance of the Fire et al. patent, which is presumed to be enabled, thousands of post-filing art references have repeatedly shown that the methods of Fire et al. work in human cells. In fact, Fire et al. won a Nobel Prize for their discovery, largely based upon the implications of its use in humans. Fire et al. recognized that double stranded RNA-mediated inhibition has advantages both in stability of the material to be delivered to the cells and the concentration required for effectiveness and further the double stranded RNA were capable of inhibiting gene expression of a target gene in a cell in vitro from an animal. Fire et al. teach the cell with the target gene may be derived from or contained in any organism, such as mammalian cells. Fire et al. recognized the methods of their invention may be used to discover the function of a target gene involved in causing or preventing a pathological condition. Fire et al. teach general concentrations of dsRNA and routes of administration and although Fire et al. does not provide evidence that dsRNA would be effective in cells such as mammalian cells, Fire

et al. is enabling because it describes the claimed method of mediating RNA interference in any cell type, specifically mammalian cells, sufficiently enough to enable a person of ordinary skill in the art to carry out the invention.

Further evidence that Fire et al. sufficiently described methods of mediating RNAi in human cells comes from Applicants instant invention because there are no manipulative differences or any structural differences used in mediating gene silencing in mammalian cells as compared to the methods disclosed by Fire et al. that serves to provide any guidance on a means of inducing a lapse in the PKR response. Applicants entire argument is drawn to the use of dsRNA that have seemingly overcome the PKR problem associated with the use of long dsRNA but it must be noted that Applicants exemplification of the use of dsRNA in mammalian cells (see Examples 1-3, specifically page 35, lines 24-25) disclose the use a 600 polynucleotide comprising a sense and an antisense sense i.e. a long dsRNA molecule. Applicants have merely reduced to practice the invention taught by Fire et al., an invention that was enabled. Even further evidence is provided by the voluminous post-filing art that have shown the methods of Fire et al. work in human cells.

Applicant further argues that the skilled artisan would not have reasonable expectation of success at using long double stranded molecules to inhibit specific target genes in mammalian cells and rely on the declaration of Dr. McCallus for the position that prior to the present invention, mammalian genes could not be targeted for sequence-specific gene expression with double stranded RNA molecules longer that 30 bases pairs.

At the outset, Dr, McCallus relies on references that relate to the effects of long dsRNA and the ability of the dsRNA to bind and activate protein kinase, which is entirely unrelated to the process of RNA interference. As stated above, Fire et al. teach general concentrations of dsRNA and routes of administration of said dsRNA and although Fire et al. does not provide evidence, i.e. reduce to practice, that dsRNA would be effective in cells such as mammalian cells, Fire et al. is enabling because it describes the claimed method of mediating RNA interference in any cell type, specifically mammalian cells, sufficiently enough to enable a person of ordinary skill in the art to carry out the invention. The use of dsRNA taught by Fire et al. would have reasonably been expected to be applicable to mammalian cells and a person of ordinary skill in the art would have had good reason, as provided by Fire et al., to pursue the known options within his or her own technical grasp i.e. taking the sufficiently described method of inducing RNAi in cells with a dsRNA and using this method to silence gene expression in mammalian cells using a dsRNA. Further, as stated above, evidence that Fire et al. sufficiently described methods of mediating RNAi in human cells comes from Applicants instant invention because there are no manipulative differences or any structural differences used in mediating gene silencing in mammalian cells as compared to the methods disclosed by Fire et al. that serves to provide any guidance on a means of inducing a lapse in the PKR response. Moreover, the instant specification does not describe using dsRNA molecules shorter than 30 base pairs, a dsRNA having 30 base pairs is not instantly claimed nor is a dsRNA having less than 30 base pairs exemplified as being capable of efficiently mediating gene silencing compared to a longer dsRNA.

Lastly, Applicants argue that the skilled artisan would not have been motivated to express several different double stranded RNAs from a single vector since it is well known in the prior art that competition between promoters (promoter interference) on a single vector resulted in unequal expression of the genes under the control of those promoters and rely on the declaration by Dr. McCallus that promoter interference was a recognized problem for the skilled artisan. Dr. McCallus relies on Hull et al. (Attachment F in the declaration filed 02/06/2008) for the assertion that "[p]romoter interference has been observed in various biological systems and has been reported to occur with RNA pol III promoters." Applicant's arguments are not convincing. A cursory review of Hull et al. would not lead the skilled artisan to believe there is a disadvantage to using more than one promoter in a vector to express multiple nucleic acid sequences. Hull et al. teach that tRNA genes that were expressed from a pol III promoter were capable of repressing the expression from adjacent downstream pol II promoters. Hull et al. teach the tRNA genes are probably responsible for the repressor function when driven by a pol III promoter. Hull et al. state there is no direct evidence that pol III promoters conclusively have a negative regulatory component and state that it seems unlikely that the pol III promoters act as repressors in all or even most instances. Nowhere in Hull et al. is it stated that multiple pol III promoters used to express different nucleic acid sequences in a vector would lead to differential expression of one gene compared to a second gene. In fact, Heifetz et al. teach expression of different nucleic acid sequences from a vector using different promoters and as stated in the previous Office action, because Calabretta et al. teach a multivalent antisense molecule targeted to two

sequences of cooperating oncogenes and teach vectors for expression of each said antisense molecules under the control of a corresponding first and second promoter for efficient endogenous expression of multiple antisense sequences in cells, it would have been obvious to one of skill in the art to make a multitargeted double stranded RNA wherein said double stranded RNA targets at least one or more than one target gene and further it would have been obvious to use expression vectors comprising two promoters for expressing said dsRNAs.

Further as stated in the previous Office action and reiterated here, although Calabretta does not teach a specific embodiment comprising construction of said construct, one of skill in the art would have been motivated to use the teachings of Calabretta et al. to construct a construct expressing different dsRNA to target multiple genes given Calabretta et al. teach simultaneous targeting of genes using two antisense compounds is advantageous to inhibit expression of cooperating proteins responsible for certain diseases. Moreover, not only would one of skill in the art been motivated to make a single vector comprising two promoters capable of expressing different dsRNA from said single vector, one would have expected success given Heifetz specifically teach construction of a single vector capable of expressing sense and antisense sequence of a dsRNA from two promoters. Therefore, the teachings of Calabretta et al. combined with the teachings of Heifetz et al. provide motivation to construct a single vector capable of expressing dsRNA from different promoters to target and silence expression from different target genes.

Thus, the rejections of record are maintained.

Conclusion

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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KC
Examiner AU 1635

/Sean R McGarry/

Primary Examiner, Art Unit 1635